Heme synthesis:

- Heme is formed of 2 parts: "protoporphyrin ring" ⊕ Fe ++
- protoporphyrin ring is formed of 4 "Pyrrole rings"
- Pyrrole ring is formed by Condensation of Glycine and succinyl Co-A
- N.B: Heme synthesis takes place in both mitochondria and cytosole → so there is no heme synthesis in the RBCs as there is no mitochondria

steps:

in Mitochondria → 2 Key regulatory steps

1. Succinyl Co-A + Glycine —(ALA synthase, $CoA.SH$)→ α-amino-βketoadipic acid
2. α-amino-βketoadipic acid —(ALA synthase, CO_2)→ δ-Aminolevulinic Acid « ALA »

- in cytosole:

3. 2 molecules of ALA —(ALA Dehydratase, $2H_2O$; Need Zn ... Lead inhibit it)→ porphobilinogen « 1st precursor of pyrrole ring »
4. 4 molecules of porphobilinogen —(uroporphyrinogen I synthase « deaminase », $4NH_3$)→ Hydroxymethylbilane (HMTB) « Linear tetrapyrrole »
5. HMB —(uroporphyrinogen III synthase « closed ring »)→ uroporphyrinogen III « tetrapyrrole »
   HMB —(Slow spontaneously)→ uroporphyrinogen I
6. uroporphyrinogen III —(uroporphyrinogen decarboxylase, $4CO_2$)→ coproporphyrinogen III

- in mitochondria:

7. coproporphyrinogen III —(coproporphyrinogen oxidase)→ protoporphyrinogen III
8. protoporphyrinogen III —(protoporphyrinogen oxidase)→ protoporphyrin III

9. protoporphyrin III « XI » —(Fe)→ Heme

Regulation of Heme synthesis:

- Remember: ALA synthase is the Key enzyme of Heme synthesis
- Heme inhibit synthesis of ALA synthase enzyme ----- « Repression mechanism ».
- ALA synthase is also inhibited by hematin « storage form of heme »
- Compartmentation of enzymes bet cytosole and mitochondria make regulation easier
- steps catalyzed by Ferrochelatase and ALA dehydratase are inhibited by Lead.
- Remember: 2/3 of heme is used for production of cytochrom 450.
- Drugs Like barbiturates induce heme synthesis for production of cytochrome P450
- Isonicotinic acid hydrazide « drugs used by TB Patients » → ⊖⊖ availability of pyridoxal Phosphate → affect heme synthesis

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Porphyrias: deficiency of one or more enzymes Concerned with heme synthesis

Causes:

1. Congenital ---- autosomal dominant except Congenetal erythropoitic porphyria
2. acquired ---- Lead Poisining ⊕ alcoholism ⊕ Liver diseases

Classification:

Porphyria is classified according to the site of defected enzyme into:

1. Erythropoitic Porphyrias: defected enzyme is in the bone marrow.
2. Hepatic " " " " " Liver
3. Mixed: " " " in both bone marrow and Liver.

hepatic porphyria is further classified as Chronic or acute.

Definition of Porphyrias:

Disease of heme synthesis Charactrized by ⊕⊕ excretion of porphyrin and porphyrin Precoursors in urine and faces and ⊕⊕ accumulation of porphrin and its Precoursors in Plasma and other tissues...

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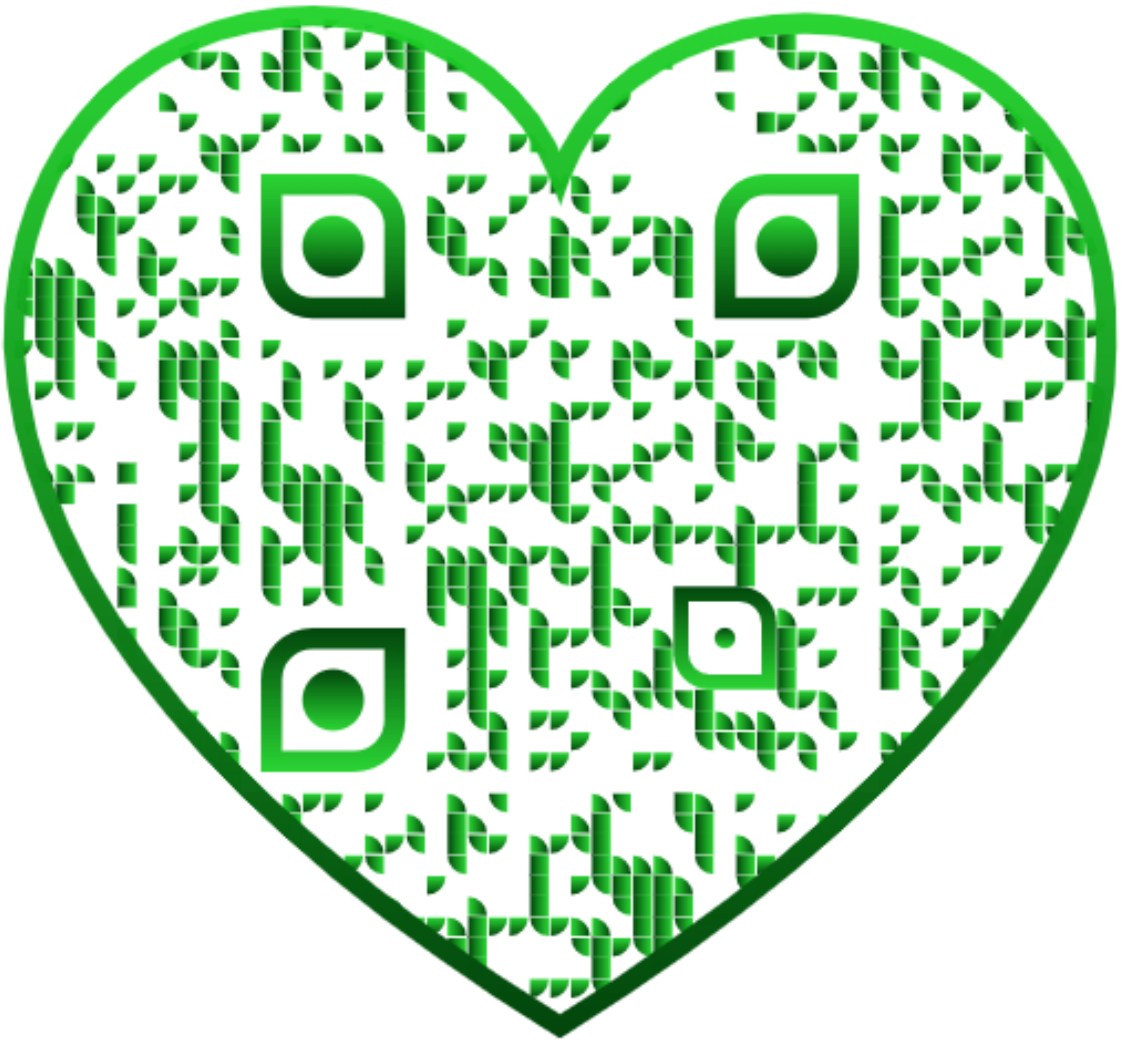

Porphyria	Deficted Enzyme	Characteristics
Hepatic		
- Acute Intermittent Porphyria	Uroporphyrinogen I synthase → accumulation of Ala & Porphobilinogen "PBG"	- Abdomenal Pain - Neuropsychiatric symptoms
- Porphyria Cutanea tarda	Uroporphyrinogen decarboxylase → ↑ uroporphyrin I, III in urine.	- photosensitivity
- Hereditary Coproporphyria	Coproporphyrinogen oxidase → excretion of coproporphrins in urine and stool	- Abdomenal Pain - Photosensitivity - Neuropsychiatric symptoms
- Variegate Porphyria	protoporphyrinogen oxidase → Coproporphrin + ALA excretion in urine & protoporphyrin in stool	- " - " - "
Erythropoitic		
- Congental Erythropoitic Porphyria "only autosomal recessive"	uroporphyrinogen III synthase → This Lead to accumulation and excretion of large amount of uroporphyrinogin I and coproporphyrinogen I	- Photosensitivity - hemolysis - splenomegally - Pink teeth
- Protoporphyria "→ accumulation of Protoporph"	Ferrochelatase	Photosensitivity

- Treatment of Congenital Erythropoietic Porphria:-
1. avoid sunlite - splenectomy.
2. blood transfusion & iron chelation therapy.
3. Bone marrow transplantation.

Disease	Cause	Laboratory findings
- unconjugated hyperbilirubinmia 1. Neonatal jaundice 2. Crigler-Najjer Syndrom I 3. Crigler-Najjer syndrome II 4. Gilbert's Syndrome	1. Newborn infant Liver is immature and can not metabolize all billirubin from RBC breakdown 2. Inhereted due to absence of UDP-Glucuronyl Transferase 3. Lack of UDP-Glucuronyl Transferase but with some activity 4. Lack of UDP-Glucuronyl Transferase, but about 80% of enzyme activity is preserved	- Level of unconjugated bilirubin is above normal "8-14 days" 2. bilirubin Level is more than 20 mg/dL - Normal Liver enzymes --- mutation is detected by "PCR" 3. indirect "unconjegated" bilirubin" 6-20" mg/dl Normal Liver enzyme and detection of mutation by PCR 4. Bilirubin level "1.2-3.0 mg/dL" Normal Liver enzymes.
- Conjugated hyperbilirubinemia	"Dubin-johnson syndrome" due to mutation of multi-drugs resistance like protein 2 (MRP2)	- Bilirubin Level "1.5-6.0 mg/dL" " direct bilirubin" - Normal Liver enzymes - Biopsy shows black pegmints in Liver
Hereditary or Primary Hemochromatosis "Bronze diabetes"	→ Mutation in HFe gene in 6th chromosome → ↑↑ uptake and storage of iron → excess absorption and saturation of Fe-binding protein and deposition of hemosidrine in tissues	→ Iron deposition in:- 1. Liver → cirrhosis 2. Pancreas → Diabetes 3. Skin → Bronze skin pegmentation
2ndry hemochromatosis	→ Repeated blood transfusion → excessive oral intake of iron.	→ Prussian blue stains on tissues → Need following investegations:- - Determination of serum ferritin by ELISA - " " " Fe and Total iron-binding Capacity "TIBC" - estimation of Con. of Hb.

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- Blood in ♂ is usually 5.5L while in ♀ is about 5L. why!?

- what are the differences between Normocyte, Macrocyte and Microcyte ---!?
  - when Mean Cell Volume "MCV" is "78-98 fL", we Call the RBC "Normocyte" which means that their size is normal
  - when size of RBC ↑, it is Called Macrocyte. On the other hand, when RBC size ↓, it is Called Microcyte.

- what is the normal Cell haemoglobin!?
  - about "27-32 Pg" → Normochromic
  - ⊕⊕ hyperchromic - ⊖⊖ hypochromic Cells

- what is the normal Con. of Hb !?
  - In ♂: 13-18 g/dl
    In ♀: 11.5 - 16 g/dl

- what are types of Hb!?

1. Normal Hb:-
   - Hb A "96-98%" ---- 2α chains ⊕ 2 β chains
   - Hb A_2 "1.5-3.2%" ---- " ⊕ 2 δ chains
   - Hb F "0.5-0.8%" ---- 2 α chains ⊕ 2 γ chains.
   - Hb A_{1c} "4-5.9%" ---- Normal "glycated" Hb.
2. Abnormal Hb:-
   - SHb ---- Valine replace Glutamic acid in 6th Position of β chain → anemia due to short Life span.
   - Hb C ---- Lysine " " " " " " " " ---- usually no symptoms, but can Lead to haemolytic anemia.
     - intact RBC with eccentric crystals of Hb C
   - Hb D ---- substitution of Glutamine for Glutamic acid of position 121 of β chain ---- Lead to mild anemia.
     - HD migrate on electrophoretic gel with Hb S but sickling test is -ve.
   - Hb E ----- substitution of Lysine for Glutamic acid in β chain Position 26 ----- Lead to mild anemia ⊕ microcytosis
3. Non Functioning Hb:-
   - Met Hb = F^{+2} is converted to F^{+3} → hypoxia → death
   - Carboxy Hb = Hb bound to Co —
   - sulf Hb = Normal Hb bound to sulfur "attach to each group" usually due to sulfonamid drugs or exposure to sulfur compounds.

- Functions "importance" of Heme ---
  1. synthesis of Hb
  2. " " Myoglobin
  3. " " Cytochrome "important in drugs metabolism"
  4. Metabolism of some enzy. e.g. Peroxidase and Catalase
  5. Metabolism " Tryptophan Pyrrolase enzyme.
  6. " of NO synthase enzyme ---

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